

## PEER REVIEW HISTORY

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## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Antipsychotic Initiation among Adults with Intellectual and Developmental Disabilities in Ontario: a population-based cohort study
<b>AUTHORS</b>	Gomes, Tara; Khuu, Wayne; Tadrous, Mina; Vigod, Simone; Cobigo, Virginie; Lunsy, Yona

## VERSION 1 - REVIEW

<b>REVIEWER</b>	Gerda de Kuijper GGZ Drenthe The Netherlands
<b>REVIEW RETURNED</b>	07-Dec-2018

<b>GENERAL COMMENTS</b>	<p>Comments</p> <p>This is a worth full study, because the authors studied a large cohort and used reliable data sources. The authors address an important issue, because there are still a lot of questions around factors influencing (ongoing ) off-label antipsychotic drug prescriptions.</p> <p>Q2. Is the Abstract accurate, balanced and complete?</p> <p>The method section in the Abstract is not clear:</p> <p>Intervention: The sentence "risk factors studied.." is not clear. The objective of the study is to investigate factors associated with initiating antipsychotics.</p> <p>Also, I wonder whether these risk factors may be called an intervention.</p> <p>Outcome measure: antipsychotic initiation among... It seems there is missing a phrase or word.</p> <p>Furthermore, in the main text, the headings Intervention and Outcomes are missing; instead there is the heading Patient Characteristics.</p> <p>Conclusions. This sentence seems to come somewhat from nowhere. Maybe the authors could mention the need for research on the relationship between antipsychotic initiation and the presence of other mental disorders, since these disorders are likely no licensed indications for antipsychotic drug prescriptions.</p> <p>Q3</p> <p>Is the study design appropriate to answer the research question?</p> <p>Yes, but the study design is not clearly described with regard to the intervention. Is this study really an intervention study or rather a retrospective cohort study?</p>
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	<p>Q5 Are research ethics addressed appropriately? It is not clear whether informed consent was needed in this study.</p> <p>Q6. Are the outcomes clearly defined? In the section Patient Characteristics a number of variables are described. Some of these variables are used as risk factors/determinants for the (primary?) outcome “Initiating antipsychotics”. Or is the primary outcome “drug exposure” during the accrual window? In the Abstract these risk factors are called “Intervention”. The authors should more clearly describe the primary outcome and secondary outcomes in this study. Furthermore, in this section: Line 45 Pg 6: Charlson Comorbidity Index: please explain Line 50 Pg 6: Medication use in the prior year included... I suppose that this medication use means use of co-medication besides the use of antipsychotics</p> <p>Q11 Are the discussion and conclusions justified by the results? In the result section the authors differentiate between antipsychotic initiation for a major mental disorder, other mental disorders and no mental disorder. In the discussion section they differentiate between presence and absence of a psychiatric condition in those starting an antipsychotic drug. They suggest that those without a psychiatric condition are prescribed their antipsychotic medication off-label. However, in those with other mental disorders these prescriptions may be off-label as well. Maybe the authors could elaborate on this issue.</p>
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<b>REVIEWER</b>	Andrea Koch Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, Technischen Universität Dresden, Germany
<b>REVIEW RETURNED</b>	18-Jan-2019

<b>GENERAL COMMENTS</b>	<p>Reviewers comments:</p> <p>BMJ Open Name: „Antipsychotic Initiation among Adults with Intellectual and Developmental Disabilities in Ontario: a population-based cohort study“ Gomes T, Khuu W, Tadrous M, Vigod S, Cobigo V and Lunskey Y Manuscript ID bmjopen-2018-028125 This paper addresses the interesting and important issue of conditions about antipsychotic initiation among adults with developmental disabilities. The study's specific objectives are to describe the factors being associated with initiating the antipsychotic treatment and patterns of persistence to antipsychotic therapy in his clientele. Thus, a large population-based cohort study with 39,244 individuals eligible for the study was conducted in Ontario. One of the main findings of this study is that 6,924 (17%) initiated an antipsychotic treatment. Of these 1,863 (26.9%) had no psychiatric diagnosis in the prior 2 years. Furthermore the factors male gender, residence in a group home, prior use of benzodiazepines, antidepressants or cognitive enhancers, a</p>
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	<p>recent emergency department visit or mental health hospitalization and a visit to a psychiatrist or family physician in the prior 90 days were significantly associated with antipsychotic initiation. Overall, this paper is well structured, written comprehensively and adds valuable and new information. I have only a few recommendations for a minor revision of the manuscript before publishing.</p> <p>In the Abstract section:</p> <ul style="list-style-type: none"> <li>- Please adhere to the journals standards regarding the structure of the Abstract.</li> <li>- Please provide a short "Background" subsection with recent study findings regarding this subject and thus leading to the objectives of this study.</li> <li>- Please summarize the Design, Setting, Participants, interventions and outcome measure in a "Methods" subsection.</li> <li>- Please complete the sentence regarding the outcome measure.</li> </ul> <p>In the Introduction section:</p> <ul style="list-style-type: none"> <li>- Please use abbreviations consistently, once they are introduced, e.g. in the last sentence (IDD; page 4).</li> </ul> <p>Materials and methods section:</p> <ul style="list-style-type: none"> <li>- page 7: Please explain, why there are different time-frames used between the different mental health services that have been utilized, e.g. regarding the number of physician visits (1year) and visits to a specialist (90 days)?</li> </ul> <p>Discussion section:</p> <ul style="list-style-type: none"> <li>- page 11: Be careful with the conclusion generalizing that the antipsychotic medication is used off-label by defining off-label use solely as the absence of a psychiatric disorder, as some antipsychotics may have an official approval to treat behavioural issues or have approved sedative effects. (This also applies to the conclusion section.) It may be helpful to provide a definition of antipsychotic medication. But as off-label use to treat behavioural problems is a common and serious issue in people with IDD, please also provide a short explanation why this study did not take this major issue into account.</li> <li>- Please provide an explanation regarding the result that people without a psychiatric diagnosis who had received multiple other medications in the year prior were more likely to be started on an antipsychotic, whereas such polypharmacy was protective against antipsychotic initiation among people with psychiatric diagnoses. Please align this result in the current literature regarding this topic.</li> <li>- Please also provide an explanation and literature classification of the results regarding the lower likelihood of antipsychotic initiation in people with comorbid metabolic and cardiovascular diagnoses.</li> <li>- Please provide a Strengths and Limitations section within the discussion section.</li> </ul> <p>Conclusion section:</p> <ul style="list-style-type: none"> <li>- I would appreciate it, if the authors could put their findings in a broader perspective. Much is said about the off-label' use in people with ID, but especially the results regarding the comorbid metabolic and cardiovascular conditions seem to be promising.</li> </ul> <p>Supplementary Appendix:</p> <ul style="list-style-type: none"> <li>- eTable1: Please provide the Diagnostic system used for the OHIP data.</li> </ul> <p>Table 1:</p> <ul style="list-style-type: none"> <li>- I would appreciate, if the authors could add a tag regarding meaningfulness of differences to the standardized differences between the two group characteristics in the table (to all values &gt; 0.10) and please also provide a short explanation of this tag in the table's footnote. Also make sure the line break in the headings is</li> </ul>
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	<p>adequate and general formatting regulations are minded in the depiction of tables.</p> <p>General recommendations:</p> <ul style="list-style-type: none"> <li>- Please shorten the manuscript slightly e.g. in the results section by avoiding redundant depiction of results e.g. in a table and in the running text (e.g. regarding table 1).</li> <li>- Please make sure, that the formatting of different headings and subheadings is consistent, e.g. regarding the different formats of the "Introduction", "Material and Methods" section vs. the "Results" and "Discussion" sections or regarding the subheadings e.g. "Data Sources" and "Patient Characteristics".</li> </ul>
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<b>REVIEWER</b>	Dr Rohit Shankar Cornwall Partnership NHS Foundation Trust & Exeter Medical School United Kingdom
<b>REVIEW RETURNED</b>	23-Jan-2019

<b>GENERAL COMMENTS</b>	<p>This is an interesting paper in an area where there is limited population based research.</p> <ol style="list-style-type: none"> <li>1. My principal concern is that the paper is written with a poor focus towards an international audience. It appears the data sets used were from Canadian insurance systems but I cannot be sure. There is a presumption that the data sets and systems used will be known internationally when that is obviously not the case. Please can an appendix be provided on the Canadian health system and what the systems used are and its specific limitations (if an insurance system then the focus I suspect will be on billing as opposed to health outcomes which could be a secondary objective).</li> <li>2. The systems used are established in the late 1980s or 1990s. Have their codes been updated alongside the changes in diagnostic criteria? If so, have all possible codes been considered?</li> <li>3. How does the prevalence established for ID compare to global prevalence of ID of 2-3 %</li> <li>4. While the authors have accepted the limitation of the diagnosis especially of ID and the degrees of ID they have coupled ID with Autism/Pervasive developmental disorder. These conditions are separate and distinct and it is preferred to have them presented separately.</li> <li>5. Drugs looked at included anti-epileptics and people with ID are known to be significantly over represented in the epilepsy population (22.5%) could this be a spurious association?</li> <li>6. It would be useful to compare the findings of their study with similar studies such as the Sheehan R et al BMJ 2015 paper which explores similar issues.</li> <li>7. I could not understand the rationale for choosing the period of study from 2010 to 2016 nor could I understand why the age was limited to 64.</li> <li>8. The authors talk of 'chromosomal disorders associated with ID' ...how was this done and identified?</li> <li>9. Premature mortality in ID is an important issue. How was this accounted for in the study period? Though small numbers expected it would be useful to know.</li> <li>10. It is said that 6,924 people were included into the study as these were the people who were initiated on antipsychotics in the 2010-2016 period and 32,000 odd not. Were those who had been</li> </ol>
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	<p>on antipsychotics prior 2010 excluded? If so how many? I am not sure this has been presented or worded correctly.</p> <p>11. It would be good to have a clear message included on how the data in future can be collected better to facilitate better research in the future.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a worth full study, because the authors studied a large cohort and used reliable data sources. The authors address an important issue, because there are still a lot of questions around factors influencing (ongoing ) off-label antipsychotic drug prescriptions.

We thank the reviewer for their supportive comments.

1. The method section in the Abstract is not clear:

- Intervention: The sentence “risk factors studied.. “ is not clear. The objective of the study is to investigate factors associated with initiating antipsychotics. Also, I wonder whether these risk factors may be called an intervention.

We thank the reviewer for this suggestion and have clarified our language, and incorporated the explanation of our modeling into the “Outcome Measures” section of the abstract, removing the “intervention” section entirely.

- Outcome measure: antipsychotic initiation among... It seems there is missing a phrase or word.

As described above, we have revised the Outcome Measure component of the abstract to provide more detail.

- Furthermore, in the main text, the headings Intervention and Outcomes are missing; instead there is the heading Patient Characteristics.

We have now added a header for the “Outcome” to the main text of the manuscript. We have not added a heading for “Intervention” as that has now been removed from the abstract. We have kept the heading for Patient Characteristics as this describes our methods for characterizing potential factors associated with antipsychotic initiation in our cohort.

- Conclusions. This sentence seems to come somewhat from nowhere. Maybe the authors could mention the need for research on the relationship between antipsychotic initiation and the presence of other mental disorders, since these disorders are likely no licensed indications for antipsychotic drug prescriptions.

We have revised the conclusion based on the recommendation by the reviewer outlined above.

Revised Text:

Factors associated with the initiation of an antipsychotic differ according to the presence of a psychiatric diagnosis. Given the long duration of antipsychotic use in this population, future research is needed to understand the appropriateness of antipsychotic initiation among adults with IDD, and the safety implications of long-term use of these products.

2. The study design is not clearly described with regard to the intervention. Is this study really an intervention study or rather a retrospective cohort study?

Thank you for raising this question – as described above, we have removed mention of an intervention throughout the manuscript.

3. It is not clear whether informed consent was needed in this study.

This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre and conducted at ICES in Toronto, Canada using deidentified data. ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act (PHIPA). Section 45 is the provision that enables analysis and compilation of statistical information related to the management, evaluation and monitoring of, allocation of resources to, and planning for the health system. Section 45 authorizes health information custodians to disclose personal health information to a prescribed entity, like ICES, without consent for such purposes. Therefore, this study did not require informed consent.

4. In the section Patient Characteristics a number of variables are described. Some of these variables are used as risk factors/determinants for the (primary?) outcome "Initiating antipsychotics". Or is the primary outcome "drug exposure" during the accrual window? In the Abstract these risk factors are called "Intervention". The authors should more clearly describe the primary outcome and secondary outcomes in this study.

We thank the reviewer for highlighting this lack of clarity in the methods. Our only outcome in the study was initiation of an antipsychotic. We have now clearly described this in our methods in both the abstract and the main text. The section describing patient characteristics includes a description of all variables included in our multivariable model.

5. Line 45 Pg 6: Charlson Comorbidity Index: please explain

The Charlson comorbidity index is a measure of patient comorbidity defined by Quan et al. in 2005 using inpatient hospital admission data. We have now included a citation to this comorbidity score in the methods.

6. Line 50 Pg 6: Medication use in the prior year included... I suppose that this medication use means use of co-medication besides the use of antipsychotics

Yes, in this section of the methods, we describe measures of medication use in the prior year for each person in the study. We explicitly outline the specific medications that we are capturing in the prior

year. We believe that this is clear as currently stated and so have not made any edits to this sentence.

7. In the result section the authors differentiate between antipsychotic initiation for a major mental disorder, other mental disorders and no mental disorder. In the discussion section they differentiate between presence and absence of a psychiatric condition in those starting an antipsychotic drug. They suggest that those without a psychiatric condition are prescribed their antipsychotic medication off-label. However, in those with other mental disorders these prescriptions may be off-label as well. Maybe the authors could elaborate on this issue.

We thank the reviewer for raising this concern. While we recognize that antipsychotics may also be used off-label among individuals without major mental health diagnoses, our data is limited in its ability to determine diagnoses of challenging behaviour, and therefore we were restricted to using absence of a diagnosed mental illness as indication of potential off-label use of antipsychotics for this reason. However, we do recognize that antipsychotics may also be used off-label to manage challenging behaviour among individuals with other psychiatric diagnoses who could also be prescribed antipsychotics to manage these conditions (e.g. depression or anxiety disorder), and this isn't captured in our analysis. We have revised the text in our discussion to address this potential.

Revised Text: Limitation Section:

Second, we cannot confirm whether antipsychotics that were dispensed to individuals without a psychiatric diagnosis were being prescribed to manage behavioural concerns, and therefore cannot draw definitive conclusions about the use of this class of medications for this indication in our study. However, the fact that individuals without a psychiatric diagnosis were more likely to be initiated on antipsychotics in family practice, and had a lower maximum dose achieved suggests that this may be the case. Furthermore, it is possible that antipsychotics are also being used off-label to manage challenging behaviour among people with psychiatric diagnoses; however we are unable to determine the indication for use in this population. It is also important to note that guidelines recommend the use of antipsychotics to manage challenging behaviour when evidence-based alternatives have been unsuccessful, and when the risk to the person or others is severe.<sup>30</sup> Using data available to us, we are unable to determine the alignment of antipsychotic use with these recommendations in this analysis. However, the high antipsychotic initiation rate and variability in use across comorbid profiles and practice settings suggest that considerable risk is being introduced to adults with IDD due to their use. Future research should investigate further the appropriateness of this prescribing and its association with harm.

Reviewer: 2

1. This paper addresses the interesting and important issue of conditions about antipsychotic initiation among adults with developmental disabilities. The study's specific objectives are to describe the factors being associated with initiating the antipsychotic treatment and patterns of persistence to antipsychotic therapy in his clientele. Thus, a large population-based cohort study with 39,244 individuals eligible for the study was conducted in Ontario.

One of the main findings of this study is that 6,924 (17%) initiated an antipsychotic treatment. Of these 1,863 (26.9%) had no psychiatric diagnosis in the prior 2 years. Furthermore the factors male

gender, residence in a group home, prior use of benzodiazepines, antidepressants or cognitive enhancers, a recent emergency department visit or mental health hospitalization and a visit to a psychiatrist or family physician in the prior 90 days were significantly associated with antipsychotic initiation.

Overall, this paper is well structured, written comprehensively and adds valuable and new information.

We thank the reviewer for their supportive comments.

2. In the Abstract section:

- Please adhere to the journals standards regarding the structure of the Abstract.
- Please provide a short “Background” subsection with recent study findings regarding this subject and thus leading to the objectives of this study.
- Please summarize the Design, Setting, Participants, interventions and outcome measure in a “Methods” subsection.
- Please complete the sentence regarding the outcome measure.

We have reviewed the journal’s abstract structure requirements and believe that the abstract as currently described aligns with their heading structure (ie objectives, design, setting, participants, intervention (if applicable), outcome measures, results, conclusion). Therefore, we have not changed the headings as outlined above, but have removed the Intervention heading as suggested by Reviewer 1, and have revised the “Outcome Measures” section to be more complete.

3. In the Introduction section: please use abbreviations consistently, once they are introduced, e.g. in the last sentence (IDD; page 4).

This change has been made.

4. Materials and methods section: page 7: Please explain, why there are different time-frames used between the different mental health services that have been utilized, e.g. regarding the number of physician visits (1year) and visits to a specialist (90 days)?

We define a number of measures of health services utilization for inclusion in our models. Specifically, we characterized the number of physician visits for any cause in the prior 1 year, as this is a measure used frequently in the literature to capture the degree of contact an individual has with the healthcare system in general. Our variable describing specialist visits was defined to provide an estimate of recent contact with a specialist which may inform the decision to initiate an antipsychotic. Therefore, we restricted this to a lookback of 90 days to ensure proximity between the specialist visit and outcome ascertainment (antipsychotic initiation).

Revised Text:

We included several measures of health services utilization, including ...number of physician visits in the prior 1 year, and recent visits to a specialist (psychiatrist or neurologist; prior 90 days).

5. Discussion section:

-page 11: Be careful with the conclusion generalizing that the antipsychotic medication is used off-label by defining off-label use solely as the absence of a psychiatric disorder, as some antipsychotics may have an official approval to treat behavioural issues or have approved sedative effects. (This also applies to the conclusion section.) It may be helpful to provide a definition of antipsychotic medication. But as off-label use to treat behavioural problems is a common and serious issue in people with IDD, please also provide a short explanation why this study did not take this major issue into account.

We thank the reviewer for this comment which is similar to one made by Reviewer #1. As we described above, our data is limited in its ability to determine diagnoses of challenging behaviour, and therefore we were restricted to using absence of a diagnosed mental illness as indication of potential off-label use of antipsychotics for this reason. Although antipsychotics are approved as adjunctive medications to treat depressive disorders and anxiety disorders, we are not aware of any antipsychotics approved for the treatment of challenging behavior or sleep disorders in IDD in Canada and therefore, by definition, their use for challenging behaviour would be considered 'off-label'. However, despite being prescribed 'off-label' in this context, we recognize that this doesn't mean that antipsychotic use to manage challenging behaviours in IDD is always inappropriate. For example, the NICE Guidelines recommend antipsychotic use in some patients when evidence-based treatment options have been exhausted and the risk to the person or others is very severe.<sup>1</sup> Therefore, although we can't measure the degree of 'appropriateness' of the antipsychotic prescribing in our databases, we believe that the high antipsychotic initiation rate and observed variability in use across comorbid profiles and practice settings suggest an important potential exposure to risk among adults with IDD. Further investigation into the appropriateness of this prescribing and its associated adverse events is warranted. We have revised the text in our manuscript to discuss this further and have added a table to the supplemental appendix outlining the included antipsychotics.

Revised Text: Limitation Section:

Second, we cannot confirm whether antipsychotics that were dispensed to individuals without a psychiatric diagnosis were being prescribed to manage behavioural concerns, and therefore cannot draw definitive conclusions about the use of this class of medications for this indication in our study. However, the fact that individuals without a psychiatric diagnosis were more likely to be initiated on antipsychotics in family practice, and had a lower maximum dose achieved suggests that this may be the case. Furthermore, it is possible that antipsychotics are also being used off-label to manage challenging behaviour among people with psychiatric diagnoses; however we are unable to determine the indication for use in this population. It is also important to note that guidelines recommend the use of antipsychotics to manage challenging behaviour when evidence-based alternatives have been unsuccessful, and when the risk to the person or others is severe.<sup>30</sup> Using data available to us, we are unable to determine the alignment of antipsychotic use with these recommendations in this analysis. However, the high antipsychotic initiation rate and variability in use across comorbid profiles and practice settings suggest that considerable risk is being introduced to adults with IDD due to their use. Future research should investigate further the appropriateness of this prescribing and its association with harm.

-Please provide an explanation regarding the result that people without a psychiatric diagnosis who had received multiple other medications in the year prior were more likely to be started on an antipsychotic, whereas such polypharmacy was protective against antipsychotic initiation among people with psychiatric diagnoses. Please align this result in the current literature regarding this topic.

We have reviewed the literature and were unable to find specific studies investigating this phenomenon. While we are unable to confirm why this different result exists between those with and without a psychiatric diagnosis, one potential explanation is that individuals with a psychiatric diagnosis may have their mental illness effectively treated with the medications that they are already being prescribed, meaning that the addition of an antipsychotic is unnecessary. In contrast, those without a psychiatric diagnosis with polypharmacy may be complex individuals with multiple comorbidities. In general, we believe that these findings highlight the fact that these two sub-populations (those with and without psychiatric diagnoses) are distinct, with different drivers of antipsychotic initiation. Future research is needed to better elucidate the specific role of polypharmacy in each of these populations.

Revised Text:

Although there was little difference in variables associated with antipsychotic initiation when considering those with and without psychiatric diagnoses separately, one important finding is that people without a psychiatric diagnosis who had received multiple other medications in the year prior were more likely to be started on an antipsychotic, whereas such polypharmacy was protective against antipsychotic initiation among people with psychiatric diagnoses. Although the specific drivers of this finding are unknown, future research should investigate the differential role of polypharmacy in antipsychotic initiation among those with and without a concurrent psychiatric diagnosis.

-Please also provide an explanation and literature classification of the results regarding the lower likelihood of antipsychotic initiation in people with comorbid metabolic and cardiovascular diagnoses.

We have slightly expanded our discussion of the metabolic findings in our study, citing literature in this population related to metabolic risks and alignment of prescribers with guideline recommendations regarding antipsychotic use in this population.

Revised Text:

Our findings have important implications for clinical practice in this vulnerable population. First, we found that the likelihood of antipsychotic initiation is lower among individuals who have a prior diagnosis for a metabolic or cardiovascular condition (e.g. diabetes, hypertension, myocardial infarction), which suggests that clinicians are aware of the literature regarding the potential risk factors for adverse events when prescribing this class of medications in this population<sup>2 3</sup> and demonstrate more caution when diabetes or hypertension are already present.

6. Please provide a Strengths and Limitations section within the discussion section.

We thank the reviewer for this suggestion. We had removed this section from the manuscript and included it in the article summary; however we now realize that it should be included in both sections. We have now re-inserted the strengths and limitations into the manuscript prior to the conclusions.

## Inserted Text (Discussion)

### Strengths and Limitations

A main strength of this study is its use of linked population-based data allowing us to study medication use and health services utilization among a large cohort of adults with IDD, regardless of how they interact with the health system. However, there are several limitations that merit emphasis. First, we relied on diagnostic codes from administrative claims databases in the prior 2 years to define the presence of psychiatric diagnoses. Although this definition is used regularly in Ontario, it has not been validated in our population of adults with IDD, and therefore it is possible that some misclassification occurred. However, given the differences observed in our stratified models, the findings from this study suggest that our definition of psychiatric diagnoses successfully identified two unique sub-populations in our cohort. Second, we cannot confirm whether antipsychotics that were dispensed to individuals without a psychiatric diagnosis were being prescribed to manage behavioural concerns, and therefore cannot draw definitive conclusions about the use of this class of medications for this indication in our study. However, the fact that individuals without a psychiatric diagnosis were also more likely to have a lower maximum dose achieved suggests that this may be the case. Furthermore, it is possible that antipsychotics are also being used off-label to manage challenging behaviour among people with psychiatric diagnoses; however we are unable to determine the indication for use in this population. It is also important to note that guidelines recommend the use of antipsychotics to manage challenging behaviour when evidence-based alternatives have been unsuccessful, and when the risk to the person or others is severe.<sup>30</sup> Using data available to us, we are unable to determine the alignment of antipsychotic use with these recommendations in this analysis. However, the high antipsychotic initiation rate, often with several other medications, and variability in use across comorbid profiles and practice settings suggest that considerable risk is being introduced to adults with IDD due to their use. Future research should investigate further the appropriateness of this prescribing and its association with harm. Third, our cohort was restricted to adults aged 18 to 64, and therefore these findings may not be generalizable to youth or older adults. Fourth, we defined new antipsychotic use on the basis of no antipsychotic prescription in the prior year. Therefore it is possible that some individuals in our cohort had more remote prior use of antipsychotics. Fifth, we are unable to study some variables that may be associated with antipsychotic initiation, including severity of intellectual disability, history of challenging behaviour, and family and paid caregiver level of stress and attitudes towards medication use. Further, we are unable to determine the degree of intellectual disability, or to specifically investigate the subgroup of individuals within the cohort with an autism diagnosis. Future research should consider further exploration into antipsychotic initiation within subsets of the IDD population. Finally, we determined residence in a group home setting using data from 2009 and assumed that this did not change over the study period. Although residence in these settings is relatively stable in Ontario, it is possible that living arrangements for some members of our cohort could have changed over the study period. Several of these limitations could be addressed through the ongoing collection and linkage of provincial health and social services data which would provide researchers with accurate estimates of IDD prevalence, living arrangements, and eligibility for public drug programs.

7. Conclusion section: I would appreciate it, if the authors could put their findings in a broader perspective. Much is said about the off-label use in people with ID, but especially the results regarding the comorbid metabolic and cardiovascular conditions seem to be promising.

We agree with the reviewer and have revised our discussion accordingly.

Revised Text:

The findings of this study suggest that, not only is antipsychotic prescribing high among adults with IDD, but factors associated with the initiation of an antipsychotic differs according to the presence of a psychiatric diagnosis and certain comorbidities. Over one-quarter of antipsychotic initiation occurred in the absence of any psychiatric diagnosis, suggesting a considerable degree of off-label antipsychotic use to manage challenging behaviour in a population with a high comorbidity and medication burden. However, in contrast, physicians appear to be more cautious in their antipsychotic prescribing to patients with pre-existing metabolic conditions, suggesting an appreciation of the potential metabolic complications associated with their use.

8. Supplementary Appendix: eTable1: Please provide the Diagnostic system used for the OHIP data.

The OHIP Diagnosis Codes are adapted from the ICD-9 classification system, but contain some differences. A footnote has been added to eTables 1 and 2 describing the source of these codes and providing a link to a document that provides detailed descriptions of each code.

9. Table 1: I would appreciate, if the authors could add a tag regarding meaningfulness of differences to the standardized differences between the two group characteristics in the table (to all values > 0.10) and please also provide a short explanation of this tag in the table's footnote. Also make sure the line break in the headings is adequate and general formatting regulations are minded in the depiction of tables.

This change has been made. All standardized differences >0.10 are presented in bolded text and a footnote has been added.

10. Please shorten the manuscript slightly e.g. in the results section by avoiding redundant depiction of results e.g. in a table and in the running text (e.g. regarding table 1).

We have reviewed our results section and have decided not to remove any of the results as originally included in the manuscript. We have made this decision because we feel that it is important to highlight important findings from the tables in the text of the document, as it helps the reader to contextualize the findings. We are also well within the word limit (3,776 of suggested 4,000 word limit) suggested by BMJ Open. If the editors feel that we should remove any of this detail to better align with journal formatting requirements, we would be happy to reconsider.

11. Please make sure, that the formatting of different headings and subheadings is consistent, e.g. regarding the different formats of the "Introduction", "Material and Methods" section vs. the "Results" and "Discussion" sections or regarding the subheadings e.g. "Data Sources" and "Patient Characteristics".

We thank the reviewer for this suggestion and have reviewed all of our headings. In its current form, the main headings are presented in bold and all capitals, with sub-headings presented in bold and lower case. We believe that this helps the reader differentiate between the journal's main headings, and our sub-headings that are specific to this study.

Reviewer: 3

This is an interesting paper in an area where there is limited population based research.

1. My principal concern is that the paper is written with a poor focus towards an international audience. It appears the data sets used were from Canadian insurance systems but I cannot be sure. There is a presumption that the data sets and systems used will be known internationally when that is obviously not the case. Please can an appendix be provided on the Canadian health system and what the systems used are and its specific limitations (if an insurance system then the focus I suspect will be on billing as opposed to health outcomes which could be a secondary objective).

We appreciate the reviewer pointing this omission out. We have now included more clarification on the data sources and their representativeness of the population in the methods, and have added a table to the supplementary appendix outlining the details on the datasets used, their coverage, main data elements and any limitations. In summary, the databases used are a combination of claims databases (capturing data for the purposes of reimbursement) and health services databases (those generated by Canadian Institute for Health Information that capture diagnoses and procedures using International Classification of Diseases [ICD] codes). Given that all health care services (including medications) are government funded for adults with intellectual and developmental disabilities, these databases allow us to capture information on all health services utilization for this population in the province.

2. The systems used are established in the late 1980s or 1990s. Have their codes been updated alongside the changes in diagnostic criteria? If so, have all possible codes been considered?

While databases were established in the 1980s and 1990s, the specific codes used to identify diagnoses and procedures have evolved over time. For example, prior to 2002, diagnoses were captured in the CIHI-DAD and NACRS databases using ICD-9 codes. Since 2002, these databases use ICD10 codes. In all of the analyses, we account for these changes and include all relevant codes.

3. How does the prevalence established for ID compare to global prevalence of ID of 2-3 %

The prevalence of adults with IDD in the HCARDD cohort is approximately 0.78%, which is similar to the prevalence for adults reported in a meta-analysis of the literature (0.49%, range 0.26% to 0.70%).<sup>4</sup> We believe that this prevalence is lower than the range suggested by the reviewer because we have focused on the adult population, where administrative prevalence is expected to be lower than in the child and adolescent population.<sup>5</sup> Because estimating prevalence has been previously reported in this population<sup>6</sup>, and because this wasn't a key objective of our study, we have not included these details in our manuscript.

4. While the authors have accepted the limitation of the diagnosis especially of ID and the degrees of ID they have coupled ID with Autism/Pervasive developmental disorder. These conditions are separate and distinct and it is preferred to have them presented separately.

We agree with the reviewer that it would be interesting to investigate these conditions separately; however unfortunately we are unable to stratify the population in this way using our data. In particular, we are unable to determine how many adults with autism also have ID or the degree of ID for each

individual. For these reasons, we have included this as a limitation of our study and area for future study.

Inserted Text (limitations):

Further, we are unable to determine the degree of intellectual disability, or to specifically investigate the subgroup of individuals within the cohort with an autism diagnosis. Future research should consider further exploration into antipsychotic initiation within subsets of the IDD population.

5. Drugs looked at included anti-epileptics and people with ID are known to be significantly over represented in the epilepsy population (22.5%) could this be a spurious association?

As the reviewer indicates, we found an association between receipt of antiepileptics and lower risk of initiation of antipsychotics. While we appreciate that people with IDD may be highly represented in the epilepsy population (as suggested by the high prevalence of anti-epileptic use in our study population), because our study is restricted to individuals with IDD (i.e. we aren't comparing to a non-IDD population), we don't believe that this should influence our findings.

6. It would be useful to compare the findings of their study with similar studies such as the Sheehan R et al BMJ 2015 paper which explores similar issues.

We agree with the reviewer that this is an important study to contrast with ours. We had previously cited this manuscript in our discussion, but now have expanded on that comparison.

Revised Text:

For example, a study by Sheehan et al<sup>7</sup> similarly found that major mental illness was associated with increased likelihood of initiating antipsychotics among adults with IDD, although they also identified a subgroup of the population who initiated antipsychotics in the absence of a psychiatric diagnosis.

7. I could not understand the rationale for choosing the period of study from 2010 to 2016 nor could I understand why the age was limited to 64.

The cohort of adults with IDD was constructed based on a diagnosis on or prior to April 1, 2009. Because we were reliant on ensuring that individuals had access to publicly funded medications, our accrual had to start after this date. We therefore chose April 1, 2010 to allow for a 1 year lookback to ensure new use of antipsychotics. Our accrual ended in 2016 as this was the most recent data available to us. The age of our study population was limited to 64 because the cohort of adults with IDD uses data from the Ontario Ministry of Community and Social Services (the Ontario Disability Support Program Database), which holds diagnostic information on all adults aged 18 to 64 years who receive ODSP income support. Therefore, we were restricted to this age range for our population.

8. The authors talk of 'chromosomal disorders associated with ID' ...how was this done and identified?

Chromosomal disorders associated with ID were identified using ICD-9 and ICD-10 codes in the CIHI databases. Specifically, these are ICD9 codes 758.0-758.39 ("Chromosomal anomalies for which a developmental disability is typically present") and ICD10 codes Q90.0-Q93.9 (excluding Q92.6). These codes capture diagnoses such as Down's Syndrome, Trisomy 21, Trisomy 18, Edwards' Syndrome, and Cri-du-chat syndrome.

9. Premature mortality in ID is an important issue. How was this accounted for in the study period? Though small numbers expected it would be useful to know.

In our main analysis, we used a cross sectional study design, and therefore all individuals were alive at their index date at which point the outcome of antipsychotic initiation was defined. In our analysis of duration of antipsychotic use, we censored all individuals on death to account for premature mortality.

Relevant Text from manuscript:

We also characterized a period of ongoing use of antipsychotics among new users of these drugs to investigate patterns of drug discontinuation over a 1 year follow-up period. We defined ongoing antipsychotic use on the basis of a prescription refill within 180 days of a previous prescription. If no such refill was found, the individual was flagged as having discontinued antipsychotic therapy, and their discontinuation date was set as the date upon which the last prescription filled would have been completed (i.e. date of dispensing plus days supply). In this analysis, we followed people forward until the first of drug discontinuation or a censoring event (death, end of observation period [March 31, 2016], or 1 year of maximum follow-up).

10. It is said that 6,924 people were included into the study as these were the people who were initiated on antipsychotics in the 2010-2016 period and 32,000 odd not. Were those who had been on antipsychotics prior 2010 excluded? If so how many? I am not sure this has been presented or worded correctly.

We thank the reviewer for raising this question. We can understand how the phrasing of our initial results may have been confusing, and have now provided more detail on the exclusion criteria in the text. These details are also outlined in eFigure 1 of the supplementary appendix. In summary, we separated the cohort into those exposed to antipsychotics during the accrual window (20,316) and those who were not (46,168). We then applied our exclusions to both groups, including the requirement that no one in either group was prescribed an antipsychotic in the 1 year prior to index. This ensured that our exposed group were new antipsychotic users, and that the unexposed group had not been previously exposed to antipsychotics in the prior year.

Revised Text:

Among the 66,484 adults with IDD in Ontario, 20,316 were prescribed an antipsychotic over the accrual period, among whom 6,924 met eligibility criteria and were new antipsychotic users. The remaining 46,168 did not have a record of an antipsychotic prescription through the public drug program over the accrual period, among whom 32,320 met our eligibility criteria.

11. It would be good to have a clear message included on how the data in future can be collected better to facilitate better research in the future.

We thank the reviewer for this suggestion, and have now added a sentence to our limitations section, outlining how improved data collection could address a number of the identified limitations of the study.

Revised Text:

Several of these limitations could be addressed through the ongoing collection and linkage of provincial health and social services data which would provide researchers with accurate estimates of IDD prevalence, living arrangements, and eligibility for public drug programs.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Andrea Koch Technische Universität Dresden Mental Health Services Research Group Department of Psychiatry and Psychotherapy Carl Gustav Carus University Hospital Dresden Germany
<b>REVIEW RETURNED</b>	10-May-2019

<b>GENERAL COMMENTS</b>	<p>Name: „Antipsychotic Initiation among Adults with Intellectual and Developmental Disabilities in Ontario: a population-based cohort study“ Gomes T, Khuu W, Tadrus M, Vigod S, Cobigo V and Lunsy Y Manuscript ID bmjopen-2018-028125</p> <p>I was grateful to review the manuscript about antipsychotic initiation among adults with developmental disabilities a second time and really appreciate the improvements made to the manuscript.</p> <p>I have the following minor revision suggestions:</p> <ul style="list-style-type: none"><li>- Please introduce abbreviations at first use (e.g. ICES, DAD, AMI, MOHLTC).</li><li>- Please elaborate the information that patient consent is not needed in this study in the manuscript according to your answer to reviewer 1's comment about this issue.</li><li>- eTable1: "Ontario Drug Benefit Claims Database":</li><li>- Please check the description section regarding the correct word usage of "opioids" and in the limitations section of "data"?</li><li>- Please be consistent within the eTable1, e.g. regarding formal aspects, consistent spelling and description of the Database Name</li><li>- eTable2: - Please complete this table and list all "other atypical antipsychotics" and all "other typical antipsychotics" encountered in this study; otherwise the information provided by this table is of little use and can be omitted.</li></ul>
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	- Maybe a general subdivision of antipsychotics (AP) into typical and atypical AP might be useful in this table.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer 2:

I was grateful to review the manuscript about antipsychotic initiation among adults with developmental disabilities a second time and really appreciate the improvements made to the manuscript.

We thank the reviewer for their thorough review.

I have the following minor revision suggestions:

- Please introduce abbreviations at first use (e.g. ICES, DAD, AMI, MOHLTC).

These changes have been made with one exception. “ICES” is not an abbreviation, but the full name of the research institute. Therefore we are unable to introduce an unabbreviated name for this organization.

- Please elaborate the information that patient consent is not needed in this study in the manuscript according to your answer to reviewer 1’s comment about this issue.

This has now been added to the revised manuscript:

Revised Text:

These datasets were linked using unique, encoded identifiers, were analyzed at ICES (www.ices.on.ca), and are used regularly to assess the drug utilization, safety and policy in the Ontario healthcare system. More details on these data sources can be found in eTable 1 in the supplementary appendix. This study was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto and conducted at ICES in Toronto, Canada using deidentified data. ICES is a prescribed entity under section 45 of Ontario’s Personal Health Information Protection Act (PHIPA) which enables analysis and compilation of statistical information related to the management, evaluation and monitoring of, allocation of resources to, and planning for the health system. Section 45 authorizes health information custodians to disclose personal health information to a prescribed entity, like ICES, without consent for such purposes. Therefore, this study did not require informed consent.

eTable1:

"Ontario Drug Benefit Claims Database": Please check the description section regarding the correct word usage of "opioids" and in the limitations section of "data"?

Thank you for noticing this – we have fixed the issues identified.

Please be consistent within the eTable1, e.g. regarding formal aspects, consistent spelling and description of the Database Name

The table has been reviewed for clarity and consistency.

eTable2:

Please complete this table and list all "other atypical antipsychotics" and all "other typical antipsychotics" encountered in this study; otherwise the information provided by this table is of little use and can be omitted. Maybe a general subdivision of antipsychotics (AP) into typical and atypical AP might be useful in this table.

This change has been made to Table 2. We have now provided the 3 routes of administration (oral, injectable and rectal) and the 2 sub-classes (typical and atypical) with a full list of included drugs.